REMARKS

Claims 1-13, and 16, all of the pending claims in this application, are rejected in the Office Action dated November 5, 2008. Claim 16 has been amended to recite that the fertility is contraception in a female. Support for the amendments to claim 16 can be found on page 2, lines 6-10 and page 25, lines 17-19 of the specification. Applicants respectfully request reconsideration of the claims in view of the foregoing amendments and the following remarks.

Before addressing the outstanding §112, first paragraph rejection, based on an alleged lack of enablement, Applicants thank the Examiner for discussing this rejection with Applicants' Attorneys on April 28, 2009. Following this discussion, the Examiner indicated in an Interview Summary mailed May 4, 2009 that no definitive conclusion was reached with respect to the enablement rejection. The Examiner also indicated in the Interview Summary that he suggested that a narrowing of the compound claims would obviate the rejection. In view of the discussion with the Examiner and further thought on this rejection, Applicants are of the opinion that amendment/a narrowing of the compound claims is not required in view of the remarks/arguments set forth below.

Claims are Enabled.

Claims 1 and 4-13 are rejected under 35 U.S.C. §112, first paragraph, because, according to the Examiner, the specification, while enabling for certain compounds, does not reasonably provide enablement for the full scope of "heteroaryl" of R^6 and R^7 nor the full scope of "heterocycloalkyl" of R^8 and R^9. Further, the Examiner asserts that a vast array of anilines are commercially available for the Skraup reaction but the substituents on R^5 (including R^7 which includes R^8 or R^9) are allegedly very numerous and questions where one can purchase or prepare the required anilines possessing these groups. Further, according to the Examiner, the Skraup reaction has been known to be sensitive to substituents on the starting aniline. In addition, the Examiner asserts that the requirement for activity at the FSH receptor provides no further guidance. According to the Examiner the only available information regarding the claimed compounds is that the compounds can be an agonist, antagonist or both for the FSH receptor. The Examiner asserts that the data submitted in the declaration by Cornelius Marius Timmers (the "Timmers

declaration") shows that some compounds bind the receptor, however the working examples are not commensurate in scope to that which is claimed. Moreover, in view of Van Straten et al.; Journal of Medicinal Chemistry 2005,48, 1697-1700, stating that "aromatic substituents in position 6 (R^6) are preferred . . ." and "space is limited because introduction of an extra t-butyl group in 11 led to a drop in potency" the Examiner asserts that there is an apparent size constraint on substituents. According to the Examiner, one could not make/use the claimed invention.

In addition, in response to applicants previous arguments, the Examiner asserts that contrary to applicants assertion that for each of the possible substituents for R^4 and R5 of the claimed tetrahydroquinoline derivatives of formula I at least one representative example is provided in the currently pending application, the examples provided are not representative. According to the Examiner R^4 is shown only as OMe, OH and H and R^6 is only ever phenyl, furan, and thiopene. According to the Examiner R^5 is the only group that has any significant variation and is only taking issue with the R^7 "heteroaryl" and the R^8 and R^9 "heterocycloalkyl" which according to the Examiner have been disclosed as phenyl, pyridine, furan, and isoxazole in the former and piperazine, pyridine, morpholine and pyrrolidine for in the later. The Examiner asserts that the disclosure of a few examples of "heteroaryl" does not enable all "heteroaryl" or "heterocyclic" on R^6 and R^5 (which is nested to R^7, which in turn is nested to R^8 and R^9).

In response, applicants submit that the various heterocyclic and heteroaryl substituent groups for R^6, and R^5, including R^7, including R^8, and R^9 are clearly defined in the specification. The definitions for heterocyclic and heteroaryl substituents as recited in the claims require a specific amount of carbon atoms and the definitions as described in the specification (see pages 4-7 of the specification) clearly describe a limited number of possible hetero atoms that may be present in the heterocycle or heteroaryl in addition to the limited number of carbon atoms. Therefore applicants submit the recitation of the terms heterocycle and heteroaryl clearly inform the skilled artisan about the scope of compounds/compositions claimed and delineates the claimed invention.

Moreover, applicants submit that for each of the possible substituents for R^5, including R^7 which includes R^8 and R^9, and R^6 of the claimed tetrahydroquinoline

derivatives of formula I at least one representative example is provided in the currently pending application. The claimed tetrahydroquinoline derivatives of formula I in independent claim 1 are clearly supported by the examples in the specification. Each one example provides a method of preparing the claimed tetrahydroquinoline derivative, including where the substituent is a "heteroaryl" or heterocycloalkyl." The claimed subject matter however does not have to be limited to only those species specifically described or exemplified but such description provides guidance for a broader genus. See, *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003); "[t]hat is not to say that the specification itself must necessarily describe how to make and use every possible variant of the claimed invention." Even with respect to unpredictable subject matter it has been well accepted that in order to satisfy the enablement requirement under 35 U.S.C. 112, first paragraph, it is not implied that "patent applicants in areas currently denominated as unpredictable must never be allowed generic claims encompassing more than the particular species disclosed in the specification." *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991). The underlying reasoning has been that even in unpredictable art it is not required to test/provide a working example for every species covered by the claim because this may require providing thousands of working examples. Not only would such requirement require the applicant/patentee to carry out a prohibitive amount of actual experiments it would also discourage inventors from seeking patent protection as the claims of such patent would be limited to only those embodiments which are expressly disclosed. *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976). Thus a single embodiment may support a generic claim, but the specification would need to enable one of ordinary skill to practice the full scope of the claimed invention by providing sufficient guidance. See, *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336 (Fed. Cir. 2005).

The current specification on pages 9-20 provides such a detailed description of methods for preparing the claimed tetrahydroquinoline derivatives of formula I to enable one of ordinary skill in the art to make the claimed invention. Specifically, the specification provides detailed guidance for preparing the R^6 substituent on the tetrahydroquinolines of the claimed invention at pages 11-13. Applicants would like to emphasize that the substituent at the R^6 position of the tetrahydroquinoline compounds of

the presently claimed are readily prepared. The addition of the appropriate acyl-intermediate is a known acylation which could be carried out by the skilled artisan by a variation of reagents/intermediates as long as the appropriate reacting group is present. See specification page 12, line 16 to page 13, line 10. For this reason, the skilled artisan would readily understand that at the R^6 position various substituents can be added without having to go through undue experimentation to determine which groups may work for the given synthesis.

Likewise, the specification provides detailed guidance for preparing the R^5 substituent with all of its variations including R^7, R^8, and R^9. At page 13, lines 12-27 specificity towards R^4 or R^5 is described as well as on page 15, line 22 to page 16, line 6 and page 19, line 3 to page 20, line 17. Preparations of compounds of the claimed invention wherein R^5 is connected through a nitrogen to the tetrahydroquinoline are provided on page 14, lines 5-14 and page 15, line 22 to page 16, line 21 by either the correct selection of anilines for the Skraup reaction which may be subsequently modified Friedel-Crafts alkylation or regioselective nitration at position 7 of the tetrahydroquinoline. The specification further provides guidance that the amino group at position 7 of the tetrahydroquinoline can be acylated with (hetero)aryl carboxylic acids, see page 16, line 23 to page 17, line 5. In addition, preparations of compounds of the claimed invention wherein R^5 is connected through an oxygen to the tetrahydroquinoline are also provided, see for example particlularly conversion of compounds of formula XXI to XXIII may be effected by acylation with the appropriate acylation agent and subsequent or simultaneous functionalization, see page 17, line 7 to page 18, line 5. Alternatively, the specification on page 20, lines 7-11 provides guidance on regioselective preparations of a triflate at position 7 (for R^5) of the tetrahydroquinoline. The triflated intermediate may be modified by known methods to prepare aminated derivatives including heteroaryl additions. For example see the description of *Wolfe, J.P. and Buchwald, S.L., Organic Synthesis,* Coll. Vol. 10, p.423 (2004); Vol. 78, p.23 (2002; Wolfe et al., Vol 10/Vol 78 see as Attachment A); and *Roger, J. and Doucet, H., Org. Biomol. Chem.* 2008, 6, 169-174 (in particular scheme 4 and table 2; See as Attachment B). Also, such heteroaryl additions through a triflate intermediate are known where a compound through orthogonically heteroaryl addition is prepared as in the claimed

invention. See WO 2006/127550, pages 32 and 33 (See Attachment C, in particular page 33, lines 1-14 and the scheme on page 32). While the aforementioned references have publication dates subsequent to the filing date of the present application (PCT filing date 2003 and provisional application filing date 2002), it is respectfully submitted that the references indicate the state of the art for such methods at the time the present application was filed (See Wolfe et al., Discussion Section, second paragraph, which also lists reference 5; See Roger et al., page 169, first paragraph indicating references 7, 8, 14 and 15; See WO 2006/127550 page 26, lines 9-10 which appears to indicate that the Suzuki reaction is known in the art.).

Therefore, in contrast to the Examiner's assertion the specification provides detailed guidance on how to prepare the claimed tetrahydroquinoline derivatives to the skilled artisan and clearly describes its possible subtituents, including heterocyclic and heteroaryl compounds having the recited amount of carbon atoms.

In addition, the specification provides in Example 51 methods of determining the activity (whether it be as an agonist or antagonist) for each of the disclosed examples. The declaration by Cornelius Marius Timmers (the "Timmers declaration") submitted previously clearly identifies activity for each of the examples described in the application, either as agonist, antagonist or both for the FSH receptor. The claimed invention is directed to compounds and compositions containing such compounds. In a recent decision by the Board of Patent Appeals and Interferences application of the enablement requirements to compounds and compositions has been reviewed in *Ex Parte Riedl*, Appeal 2008-3178 (BPAI, Sept. 23, 2008). The Board decided that were compounds and compositions are concerned the specification is required to enable one of skilled in the art to make the compounds and compositions and to provide some credible use. A sufficiently clear and detailed description is required to enable the skilled artisan to make the claimed compound or composition. However, in *Ex Parte Riedl* the Board determined that providing some credible use is all that is needed when the claimed invention is directed to compounds. Thus, applicants were not required to show for each of the compounds claimed whether they would be successful in the treatment of osteoporosis. The Board reasoned that the claims were not directed to a method of treating osteoporosis and the claimed compounds were shown to have an effect on the

kinase signalling pathway that is known to be linked with osteoporosis. Similarly to *Ex Parte Riedl*, the claimed invention is directed to compounds and compositions, the preparation for which has been clearly described in the specification to one of skill in the art as discussed above. Further, as discussed these compounds and compositions have been shown to be either an agonist, antagonist or both for the FSH receptor (see also Timmers declaration), an important hormonal receptor linked to fertility. For these reasons, applicants submit that the specification clearly describes to one of skill in the art how to make the compounds and composition of the claimed invention and provides a credible use therefore having been shown to interact with the FSH receptor, a known receptor in regulating fertility.

Thus, Applicants submit that the specification provides an enabling disclosure for the claimed tetrahydroquinoline derivatives of formula I describing at least one synthetic method for such derivative, including those where in R^6 or R^5 (in which R^7, R^8, and R^9 are embedded) the substituent is a heteroaryl or heterocycloalkyl, as well as showing activity with respect to the FSH receptor. For these reasons applicants submit that the skilled artisan reading the disclosure of the currently pending application would know how to make and/or use the claimed invention. Accordingly, Applicants submit that claims 1, and 4-13 are clearly enabled by the specification as filed and respectfully request withdrawal of the rejection of claims 1, and 4-13 under 35 U.S.C. §112, first paragraph.

Claim 16 is rejected under 35 U.S.C. §112, first paragraph for failing to comply with the enablement requirement. The Examiner asserts that while the claim is directed to a method of fertility regulation there is no nexus between the claimed compounds and methods of fertility regulation as set forth on pages 3-4 and 10-13 of the Office Action and as previously asserted. The Examiner maintains the rejection because the paucity of data in the specification, the relatively poorly developed understanding of the effect of FSH receptor agonists/antagonists, and the myriad of different physiological functions encompassed by the term "fertility regulation" clearly warrant the conclusion of lack of enablement. Further, and as previously asserted by the Examiner the FSH receptor, a G-protein coupled receptor with a vast number of binding sites and conformations, may be associated with distinct physiological outcomes depending on the

binding site that is activated. In view of this statement the Examiner refers to Guo, Tao; Expert Opinion on Therapeutic Patents 2005, 15(11), 1555-1564, stating that only in the clinic will the question of whether a small molecule FSH receptor modulators will be successful as fertility agents be answered. According to the Examiner there is no successful use of the compounds in the claimed method in an animal model and no clear correlation between antagonism of this receptor and a therapeutic outcome. The Examiner also refers to a passage in the Kenakin et al. article, "The ligand paradox between affinity and efficacy: can you be there and not make a difference", TRENDS in Pharmacological Sciences, 2002, 23, 275-280", to allegedly show that in the present case "we have exactly this situation, namely a ligand with affinity, but not known function, which as Kenakin et al. concluded ". . .the discovery of macro-affinity of a ligand for a receptor should be considered only a starting point for the optimal exploitation of a drug for therapeutic utility."

In response, applicants submit that the claimed tetrahydroquinoline derivates of formula I are shown to be ligands for the FSH receptor, as demonstrated in Example 51 of the specification of the currently pending application and in Table 1 of the previously submitted declaration by Cornelius Marius Timmers (the "Timmers declaration"). Moreover, enablement is not limited to particular working examples and the need for some experimentation is not enough to establish a lack of enablement as long as the required experimentation is reasonable (not undue). Applicants submit as previously presented that the specification provides clear guidance with respect to assaying antagonistic activity for the compounds of the claimed invention. Such antagonistic activity to the FSH receptor is also shown for the examples in the Timmers declaration. FSH receptor activation through FSH in women is a well described pathway in regulating fertility. Thus, applicants submit there is a clear nexus between the observed activity of the claimed tetrahydroquinoline derivatives of formula I as antagonist and a method of regulating fertility wherein the regulation of fertility is contraception in women. For these reasons, Applicants submit that the specification provides an enabling disclosure for the claimed tetrahydroquinoline derivatives of formula I describing a method for determining as well as showing inhibition of the FSH receptor activity and thereby also the corresponding decrease in fertility. Thus,

Applicants submit that the skilled artisan reading the disclosure of the currently pending application would know how to make and/or use the claimed invention of claim 16, providing an enabling disclosure to the skilled artisan for where the regulation of fertility is contraception in females.

For the above reasons, Applicants submit there is a nexus between the claimed compounds and methods of fertility regulation as in claim 16. Accordingly, Applicants submit that claim 16 is clearly enabled by the specification as filed and respectfully request withdrawal of the rejection of claim 16 under 35 U.S.C. § 112, first paragraph.

Double Patenting Rejection.

Claims 1, 4-13, and 16 are previously provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 4, 7, 10-21, and 23 of co-pending application 10/482,707 and over claims 1-8, and 11 of co-pending application 10/540,335. According to the Examiner, although the wording of these allegedly conflicting claims is not identical they are not patentably distinct because there is substantial overlap in scope of the claims. The Examiner notes that the wording is only slightly different and that the '707 application is broader and the '335 application is narrower.

In response to the obviousness-type double patenting rejection of claims 1, 4-13, and 16 over claims 4, 7, 10-21, and 23 of co-pending application 10/482,707 ("the '707 application"), Applicants submit, as previously argued, that the claimed tetrahydroquinoline derivatives of formula I are very different from the compounds in claims 1-9 of the co-pending '707 application. In the currently claimed invention the tetrahydroquinoline derivatives of formula I require that **both** positions 5 and 7 of the benzene ring of the bicyclic tetrahydroquinoline are substituted with R^4 and R^5 respectively, whereas the compounds in the '707 only require **one** substituent on any one of positions 5, 7 and 8 of the same benzene ring. If however one of these substituents in the claimed invention is hydrogen, R4 may be H, the other substituent (R^5) is selected from amino, (di)(1-4C)alkylamino, (2-5C)heteroarylcarbonylamino, (2-5C)heteroarylcarbonyloxy, R^8-(2-4) alkoxy, R^9-methylamino or R^9-methoxy, all of which

differ substantially from the possible substituents disclosed in the '707 application for this position. The Examiner's reliance on an alleged "very close" structural similarity from *In re Grabiak* 226 USPQ 870 and "a known compound may suggest its analogs or isomers" from *In re Deuel* 34 USPQ2d 1210, is unfounded. As described above the substituents on R^5, when R^4 is H, differ substantially from those in the '707 application at the position R^7, and the compounds disclosed in the '707 application do not provide for more than one substitution on the benzene ring of the tetrahydroquinoline. There is no teaching or suggestion in the '707 application that the 5, 7, and 8 positions of the benzene ring of the tetrahydroquinoline compound disclosed therein can be substituted as in the claimed invention. Accordingly, Applicants submit that, in contrast to the Examiner's assertions, there is no overlap between the claimed compounds and the compounds in claims 4, 7, 10-21, and 23 of the co-pending '707 application nor does the disclosure in the '707 application teach or suggest the claimed tetrahydroquinoline derivatives.

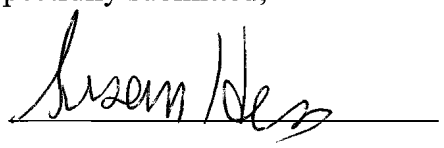
For this reason Applicants respectfully request withdrawal of the provisional rejection of claims 1, 4-13 and 16 under the non-statutory doctrine of obviousness type double patenting.

In response to the obviousness-type double patenting rejection of claims 1, 4-13, and 16 over claims 1-8, and 11 of co-pending application 10/540,335, Applicants defer responding to the rejection until such time as any of the above claims is allowed at which time applicants, although disagreeing with the Examiner's assertions, intend to submit a proper Terminal Disclaimer.

In view of the above amendment, Applicants believes the pending application is in condition for allowance. If the Examiner believes a telephone conference would be of value, he is requested to call the undersigned at the number listed below. Applicants respectfully request the issuance of a timely Notice of Allowance in the case.

Dated: May 5, 2009

Respectfully submitted,

By 

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